Rheumatoid arthritis

Rheumatoid arthritis

- Chronic multisystem disease
- Unknown cause
- Characteristic feature – persistent inflammation of synovia in symmetric peripheral joints
- Synovial inflammation → cartilage damage and bone erosions → deformation and functional impairment of joints
- Course variable:

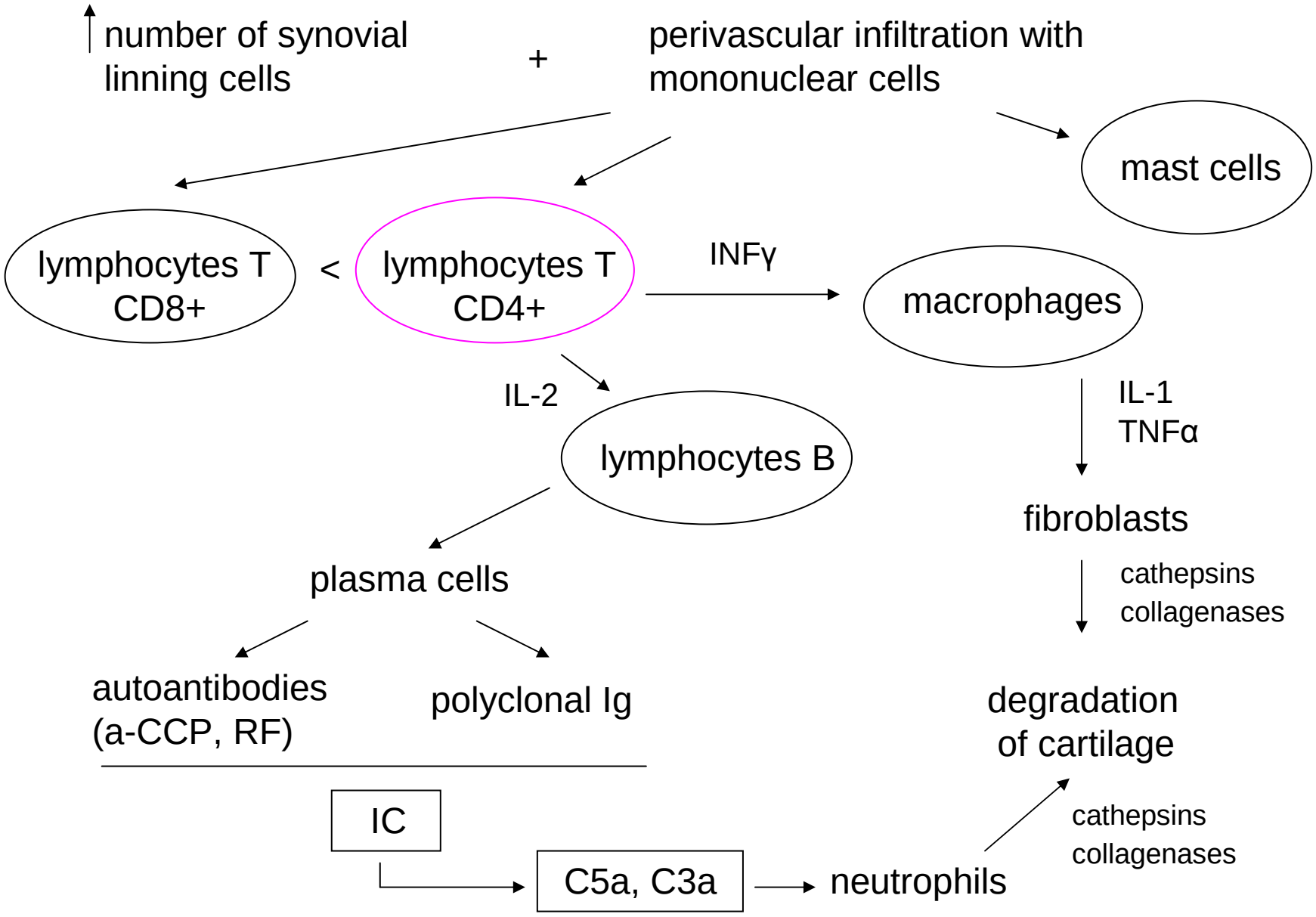
  mild oligoarticular illness ←→ progressive severe damage

Rheumatoid arthritis

- Women affected 3x more often than men
- Onset in the 4th or 5th decade
- Genetic predisposition: first-degree relatives are 4x more often affected
- Class II major histocompatibility complexallele HLA-DR4 – major genetic risk factor for RA
- Role of environmental factors: RA might be a manifestation of a response to infectious agent in genetically susceptible individuals

Characteristic features found on microscopic examination of synovia include:

- hyperplasia and hypertrophy of the synovial lining cells
- vascular changes: microvascular injury, thrombosis, neovascularisation
- edema
- infiltration with mononuclear cells – lymphocytes T, lymphocytes B, plasma cells, mast cells
- activation of macrophages, fibroblasts and neutrophils


number of synovial linning cells
+
perivascular infiltration with mononuclear cells
mast cells
lymphocytes T CD8+
<
lymphocytes T CD4+
INFγ
macrophages
IL-2
IL-1
TNFα
lymphocytes B
fibroblasts
plasma cells
cathepsins
collagenases
autoantibodies (a-CCP, RF)
polyclonal Ig
degradation of cartilage
IC
C5a, C3a
neutrophils
cathepsins
collagenases

- Cartilage distruction- result of release of many proteolytic enzymes, but the main culprit is inflamed synovium called pannus, which spreads within the joint and cover the cartilage

- Inflammatory cytokines - responsible for clinical manifestation of RA: malaise, fatigue, osteoporosis, elevated serum acute-phase reactants

Clinical systemic symptoms:

- Onset is insidious: prodrome symptoms (weeks/months)
- General weakness, anorexia, fatigue
- In 10% the onset is acute with acute polyarthritis, fever, lymphadenopathy, splenomegaly

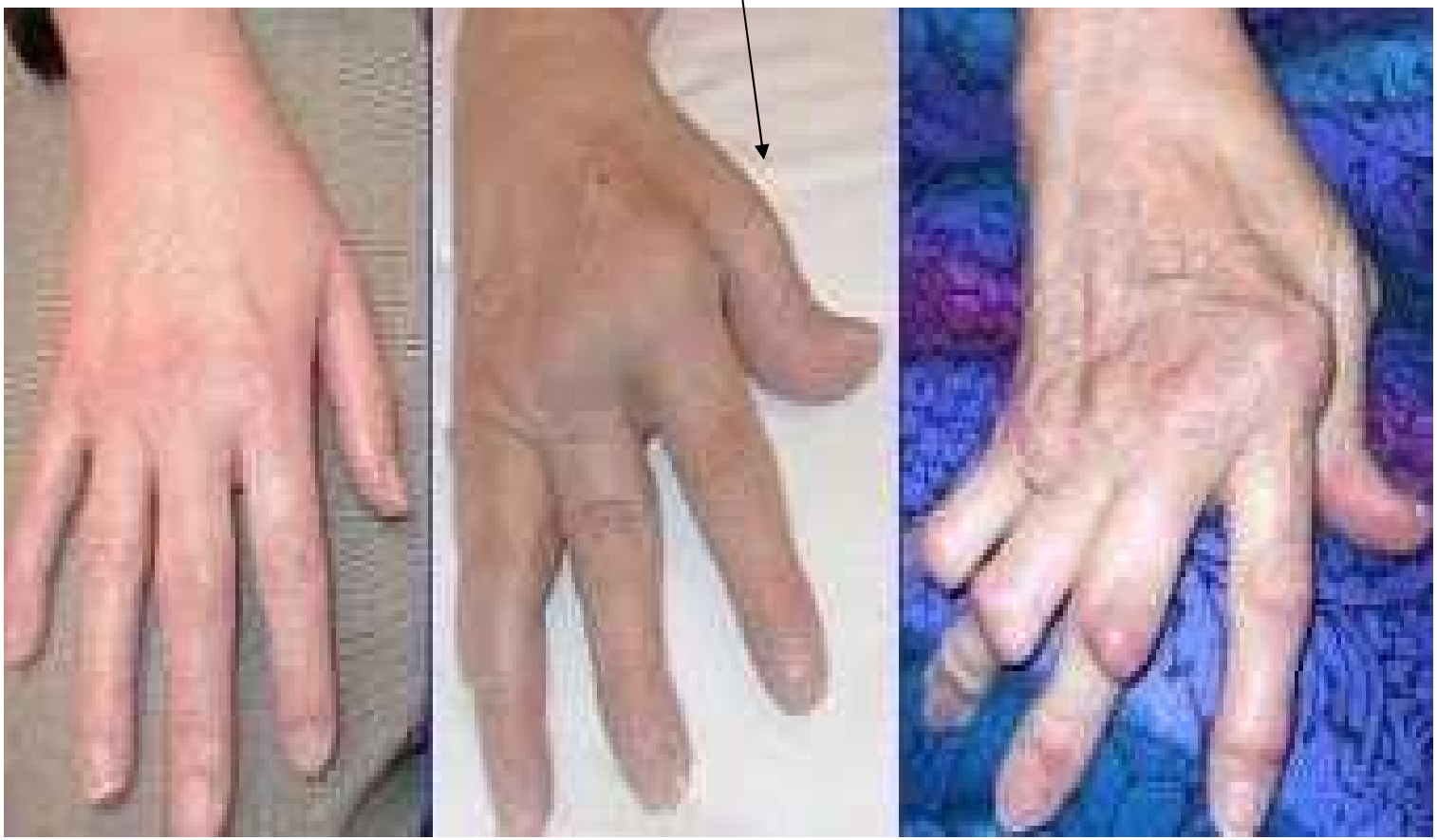
Specific symptoms:

- Pain (aggrevated by the movement), swelling, tenderness of joints, limitation of motion
- Morning stiffness >1 hour duration (common, but not patognomonic for RA)
- Joint is warm, held in flexion, skin is unchaged
- Polyarthritis developes gradually in symmetric joints: hands, wrists, knees, feet; initially it can be confined to several joints

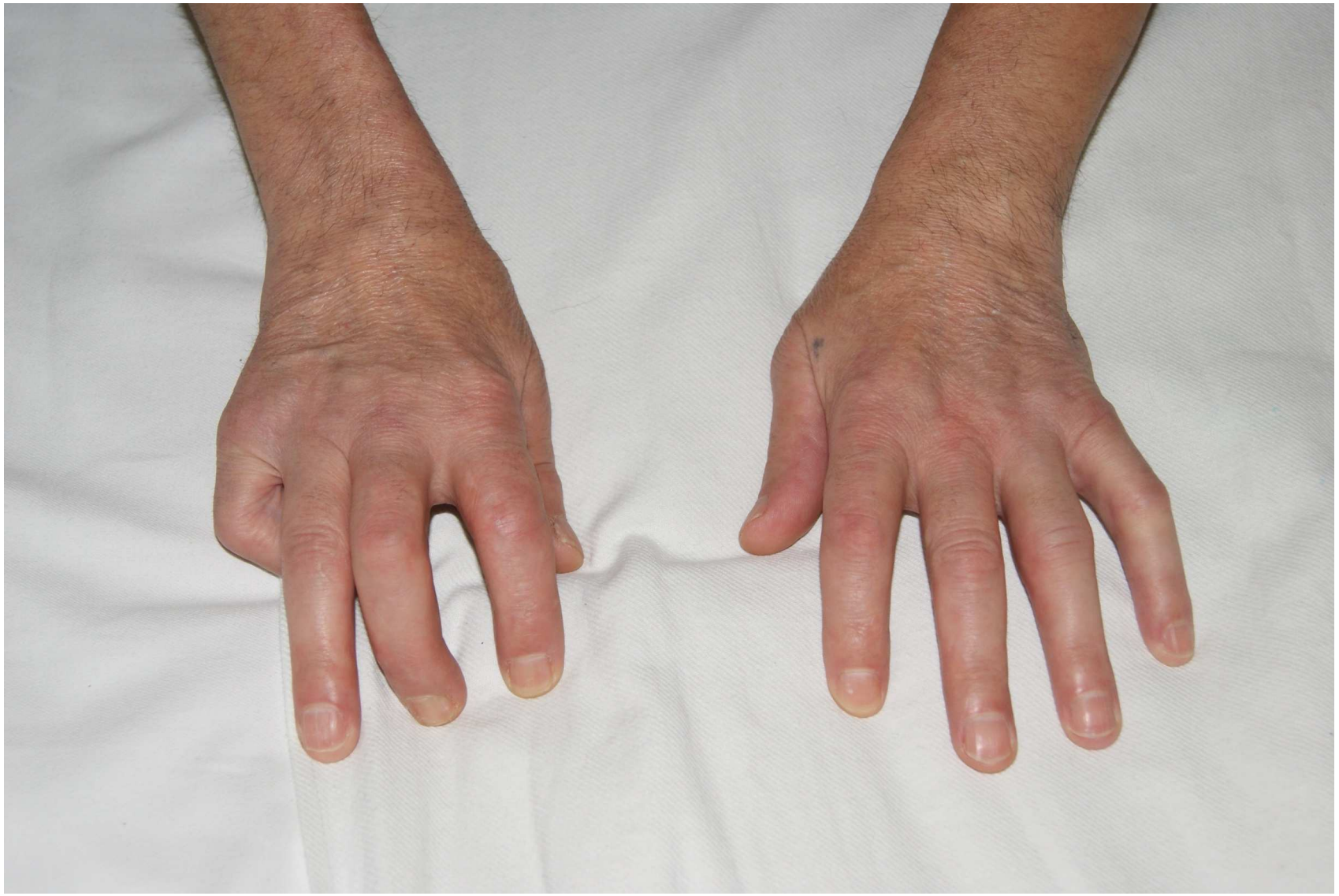
Changes in hands are localized at the wrist, metacarpophalangeal joints, proximal interphalangeal joints and include:

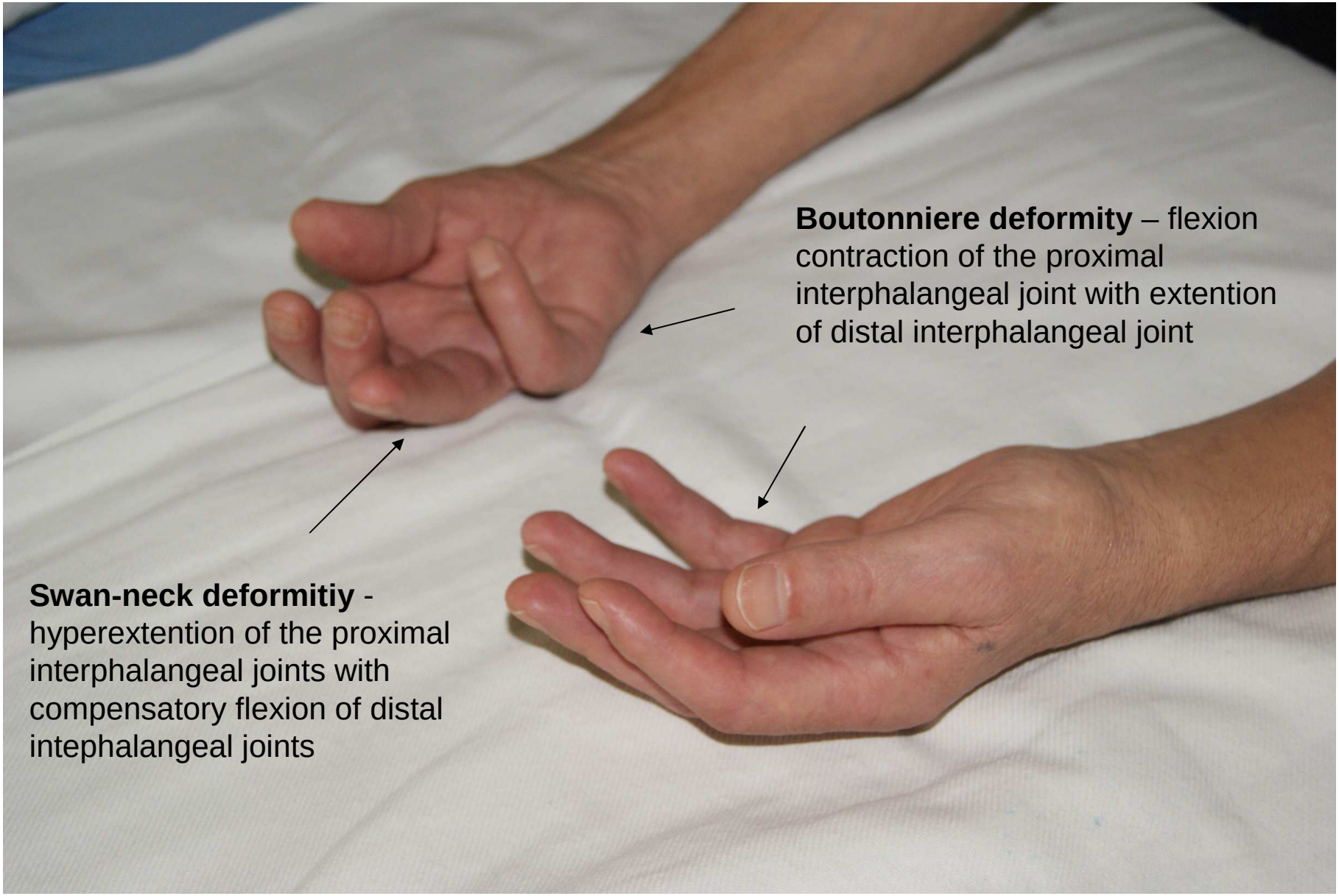
Hyperextension of the 1st interphalangeal joint and flexion of the 1st metacarpophalangeal joint (loss of thumb mobility and pinch)

Radial deviation at the wrist and ulnar deviation at the digits

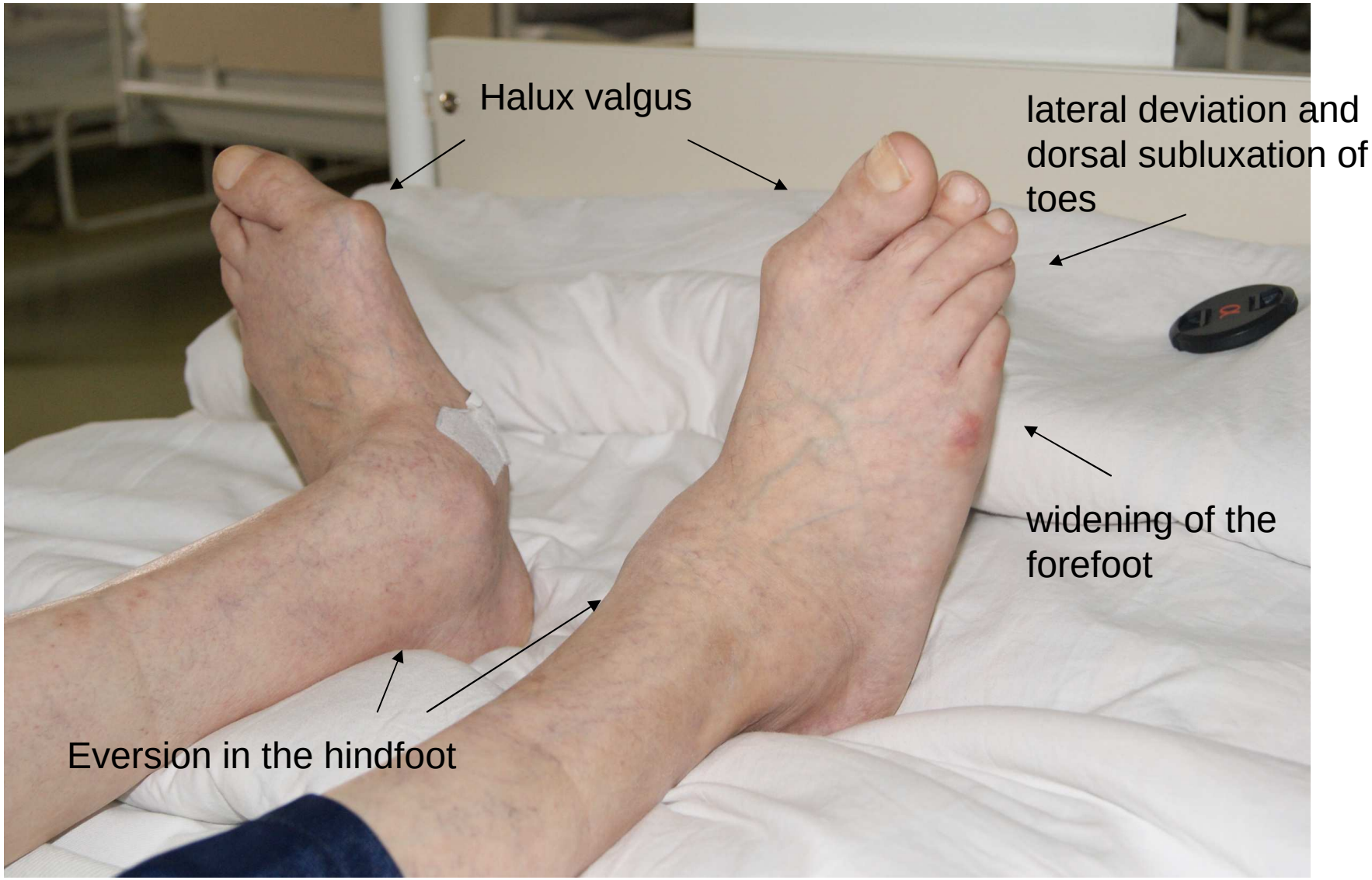


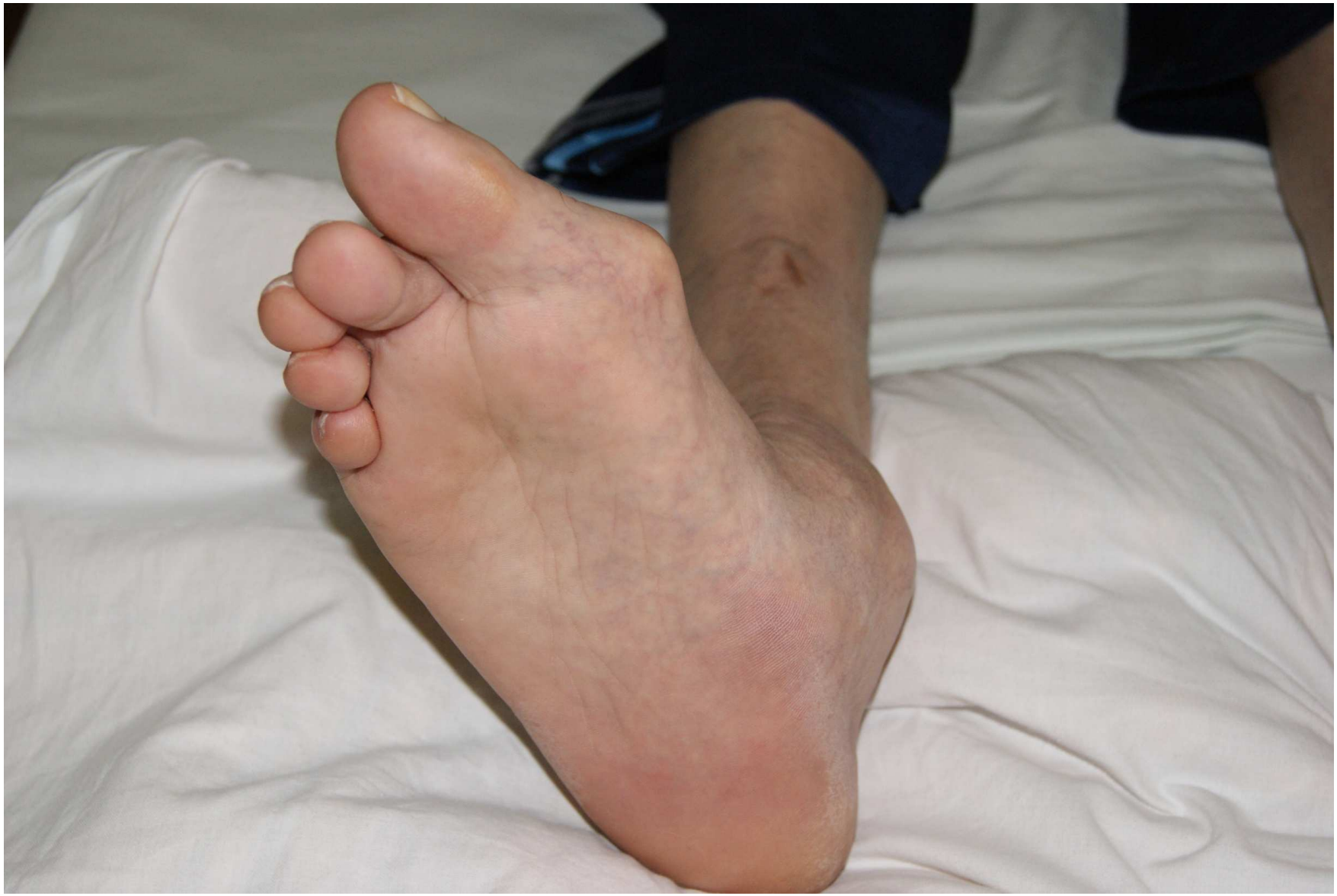
Radial deviation at the wrist and ulnar deviation at the digits



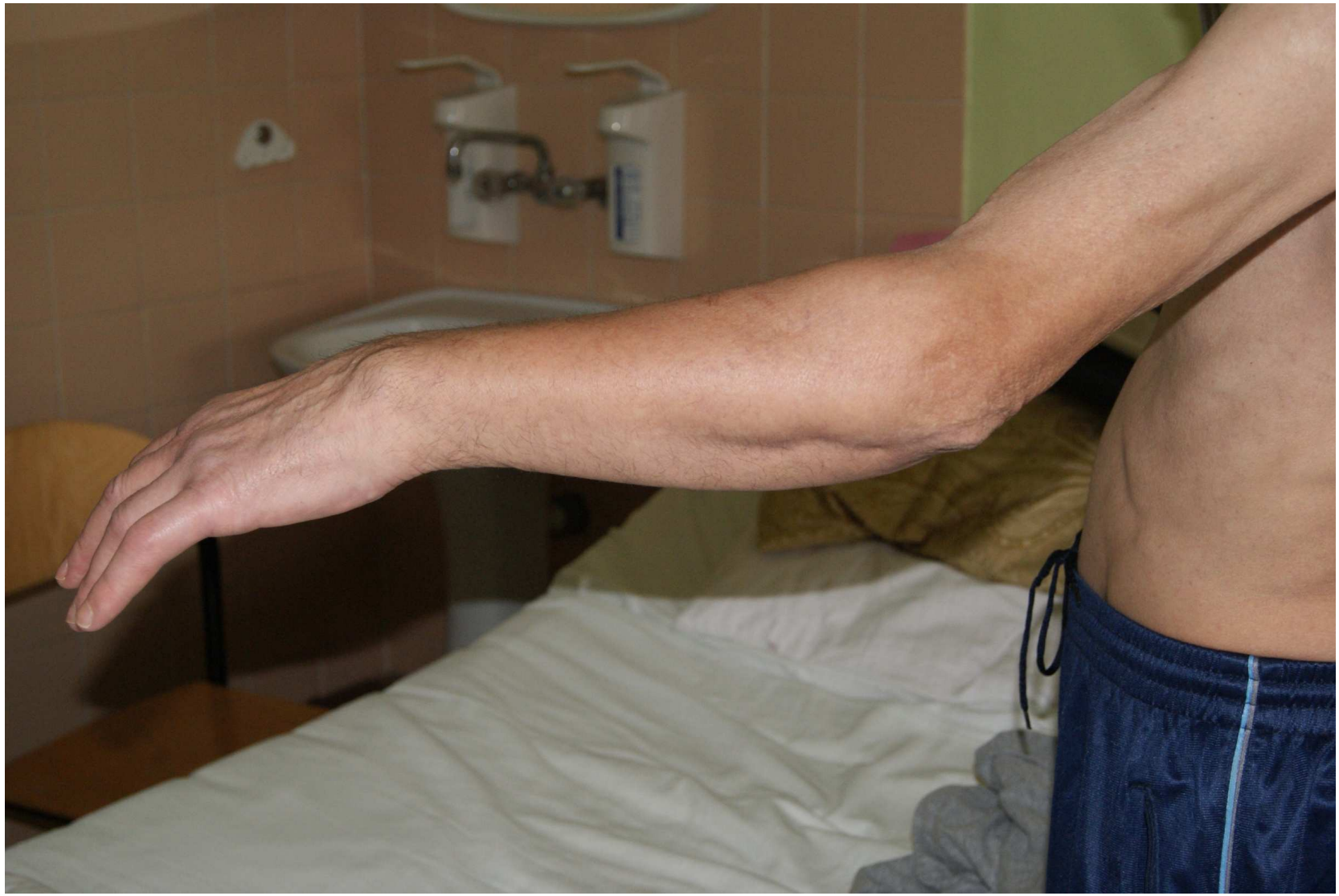

Boutonniere deformity – flexion contraction of the proximal interphalangeal joint with extention of distal interphalangeal joint
Swan-neck deformitiy - hyperextention of the proximal interphalangeal joints with compensatory flexion of distal intephalangeal joints

Arthritis of forefoot and ankles – produces severe pain and number of deformities

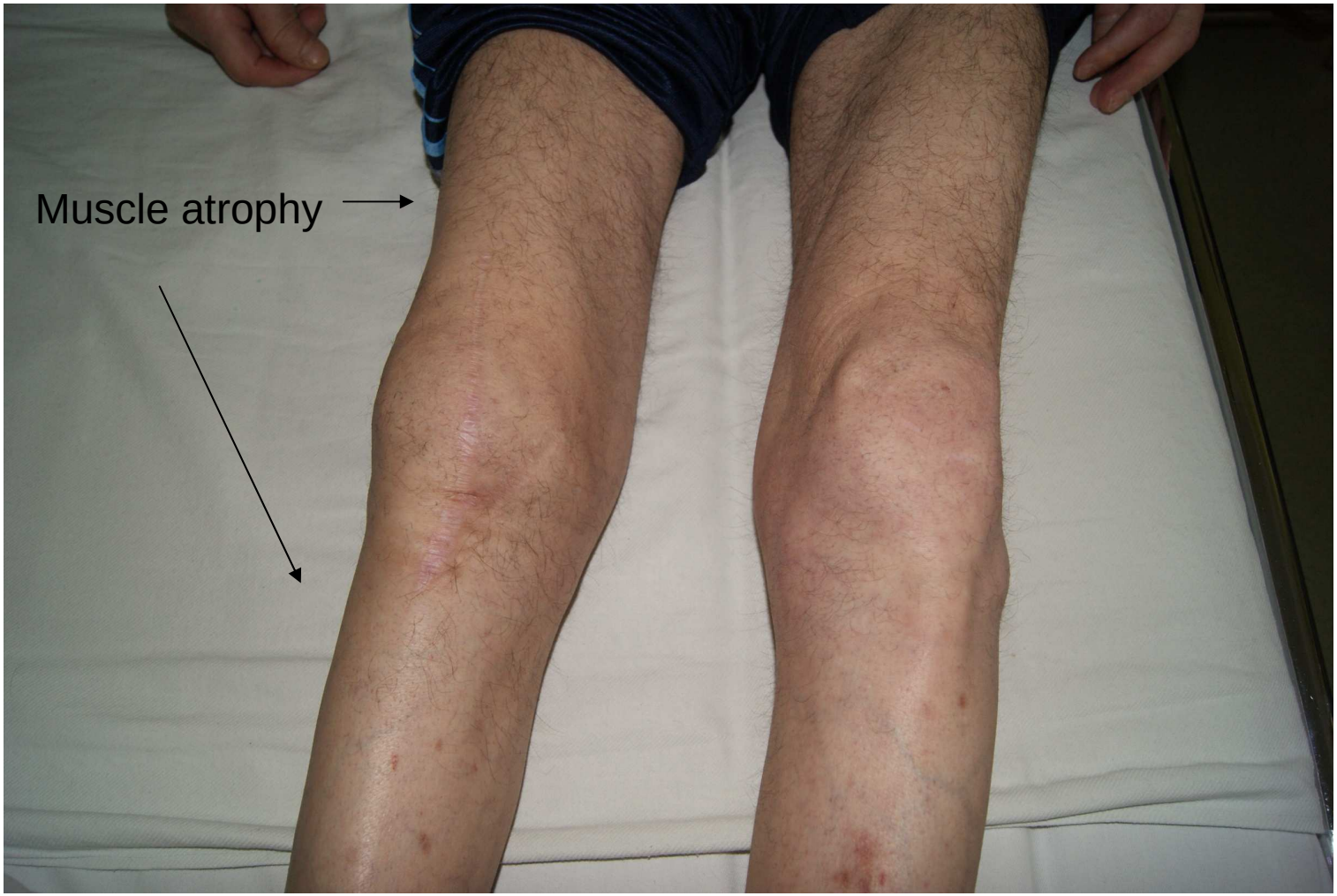


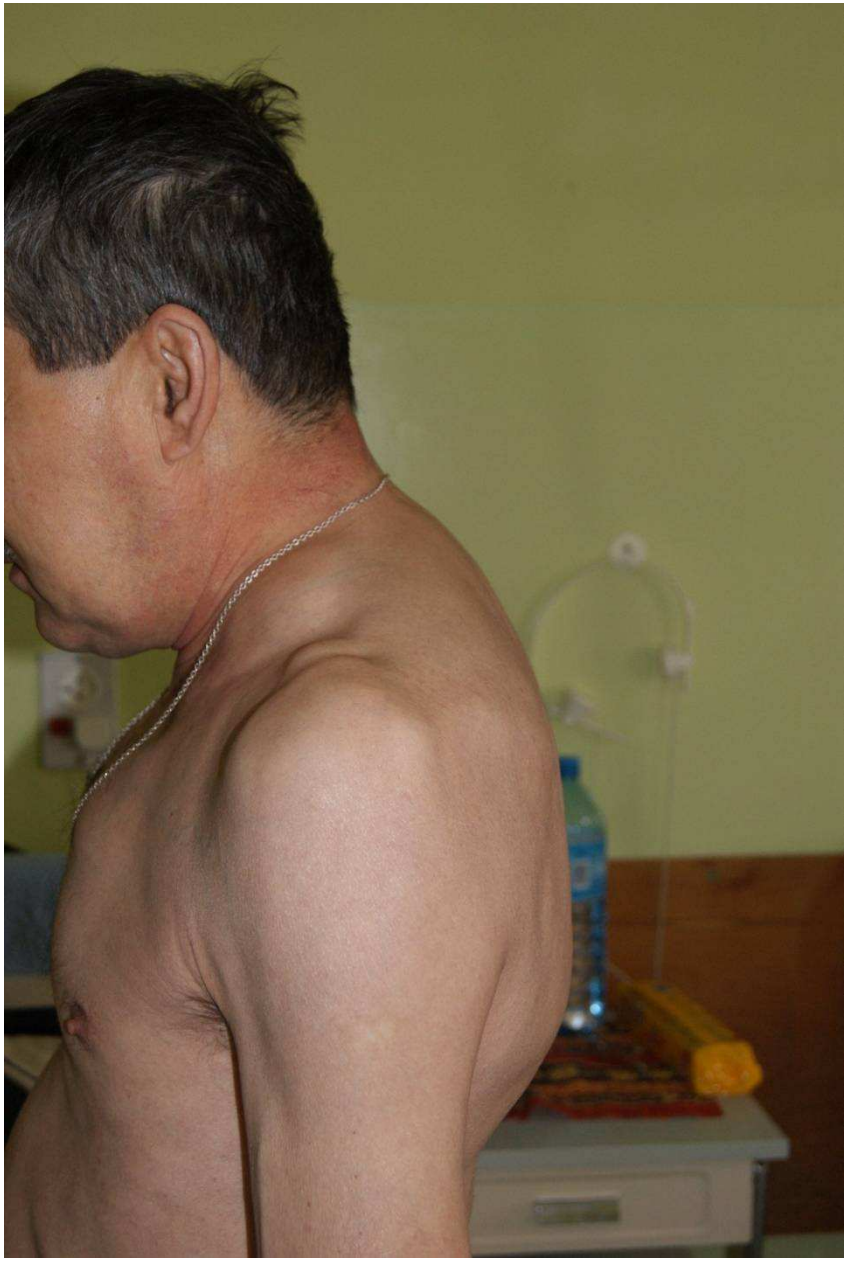


Synovitis of elbow – leads to flexion contractions



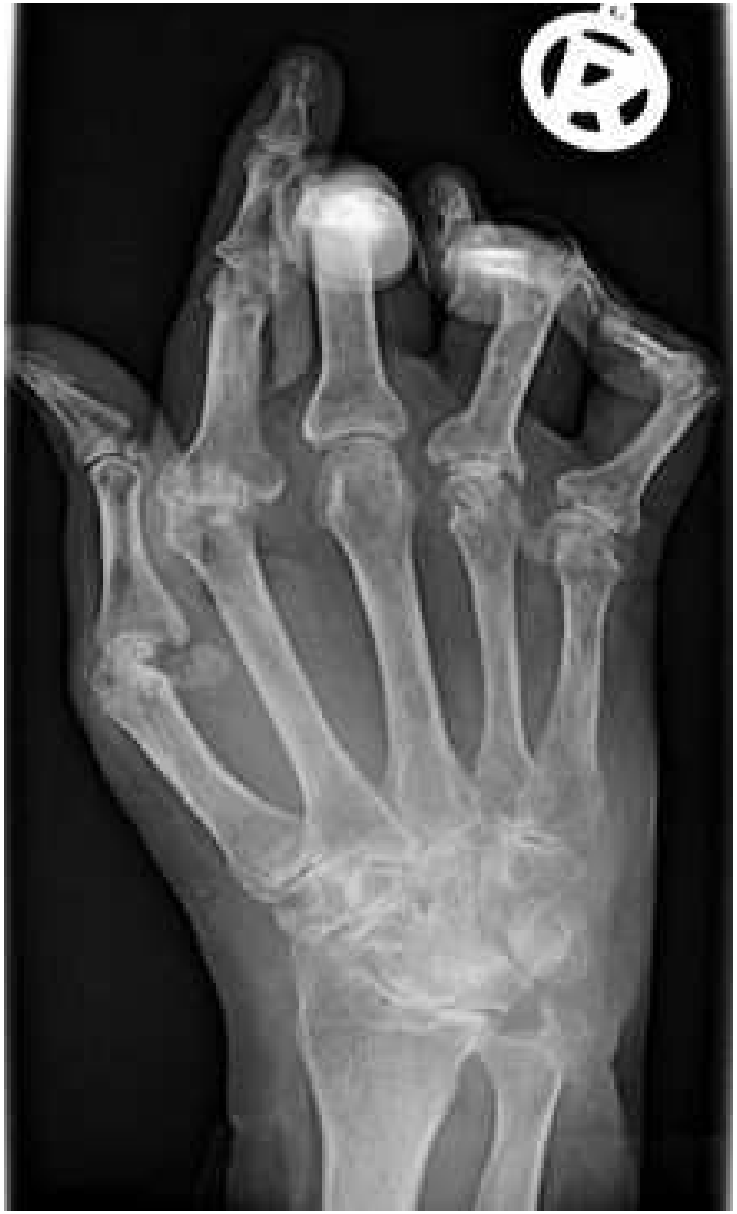
Knee – is commonly affected, with hypertrophy of synovium, which creates Baker's cyst – extension of synovium into the popliteal space





Axial skeleton – affected rarely, limited to upper cervical spine

→ atlantoaxial subluxation
→ occiput pain
→ compression of the spinal cord



Radiographic signs:

- symmetric location

-iuxaarticulat osteopenia

- loss of articular cartilage

- bone erosions

Rheumatoid arthritis

RA – systemic disease with extraarticular manifestations (in individuals with high titers of rheumatoid factor:

- Atrophy of skeletal muscle approximate to affected joints
- Rheumatoid nodules – found on periarticular structures, areas subjected to mechanical pressure, pleura, meninges – anywhere – they localize on the basis of local vasculitis, created of the collagen fibres, macrophages and granulation tissue.
- Rheumatoid vasculitis – can affect any organ: polyneuropathy, skin ulceration, visceral infarction
- Pulmonary manifestations: rheumatoid nodules in pleura and lungs, interstitial fibrosis → impairment of the diffusing capacity of the lungs, pulmonary hypertension
- Asymptomatic pericarditis
- Peripheral neuropathy- due to vasculitis
- Felty's syndrome – chronic RA, splenomegaly, neutropenia (< 1500 cell/ul), in individuals with long-standing disease; → increase risk of infections
- Osteoporosis – effect of inflammatory cytokines, distruction in bones, and side-effect of glucocorticoids
- Amyloidosis – chronic renal failure

Laboratory findings - no test is specific for diagnosing RA, but:

- 2/3 patients with RA are RF (rheumatoid factor) positive
  RF is an autoantibody IgM reactive with Fc portion of IgG
- high titers of RF – severe and progressive disease with extraarticular manifestation
- 5% healthy persons are RF positive, frequency in healthy population increases with age
- RF present in SLE, Sjögren's syndrome, chronic liver diseases
- RF does not establish the RA diagnosis !!! – confirms a diagnosis when suggestive clinical presentation

• Anti-CCP antibodies – to cyclic citrullinated polypeptides
- sensitive and more specific test than RF
- found in 1,5% healthy persons, does not predict RA

• Normochronic and normocytic anemia – ineffective erytropoiesis

• Thrombocytosis → they correlate with activity of disease (ESR and CRP levels inceased)

• Synovial fluid – inflammatory fluid (high concentration of protein, high white cell count)

Establishing the diagnosis:
ACR criteria 1987 (demonstrate to 94% sensitivity, 89% specificity)
a-d present at least 6 weeks; b-e observed by the physician

Table 314-1 The 1987 Revised Criteria for the Classification of RA
1. Guidelines for classification
a. Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA).
b. Patients with two or more clinical diagnoses are not excluded.
2. Criteria[a]
a. Morning stiffness: Stiffness in and around the joints lasting 1 h before maximal improvement.
b. Arthritis of three or more joint areas: At least three joint areas, observed by a physician simultaneously, have soft tissue swelling or joint effusions, not just bony overgrowth. The 14 possible joint areas involved are right or left proximal interphalangeal, metacarpophalangeal, wrist, elbow, knee, ankle, and metatarsophalangeal joints.
c. Arthritis of hand joints: Arthritis of wrist, metacarpophalangeal joint, or proximal interphalangeal joint.
d. Symmetric arthritis: Simultaneous involvement of the same joint areas on both sides of the body.
e. Rheumatoid nodules: Subcutaneous nodules over bony prominences, extensor surfaces, or juxtaarticular regions observed by a physician.
f. Serum rheumatoid factor: Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.
g. Radiographic changes: Typical changes of RA on posteroanterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

Treatment of RA:

- relief of pain and reduce inflammation: NSAIDs, analgesics, low dose of oral glucocorticoids

- protection of joints and control systemic manifestation:

- a) DMARDs (disease-modifying anti-rheumatic drug) – methotrexate, sulfasalazine, chloroquine, gold salts, d-penicillamine

- b) Biologics:
- neutralizing TNF – infliximab, etanercept, adalimumab;
- neutralizing IL-1 - anakinra
- depletion of B cells – rituximab

- c) Immunosuppressive drugs – leflunomide, cyclophosphamide, cyclosporine, azathioprine